Reply to "Comment on 'Regularizing Capacity of Metabolic Networks' "

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In a recent paper [C. Marr, M. Müller-Linow, and M.-T. Hütt, Phys. Rev. E **75**, 041917 (2007)] we discuss the pronounced potential of real metabolic network topologies, compared to randomized counterparts, to regularize complex binary dynamics. In their comment [P. Holme and M. Huss, arXiv:0705.4084v1], Holme and Huss criticize our approach and repeat our study with more realistic dynamics, where stylized reaction kinetics are implemented on sets of pairwise reactions. The authors find no dynamic difference between the reaction sets recreated from the metabolic networks and randomized counterparts. We reproduce the author's observation and find that their algorithm leads to a dynamical fragmentation and thus eliminates the topological information contained in the graphs. Hence, their approach cannot rule out a connection between the topology of metabolic networks and the ubiquity of steady states.

PACS numbers: 82.39.-k, 89.75.Kd, 05.45.-a

In a recent investigation [1] we study transient dynamics on abstract representations of metabolic networks. Our binary threshold dynamics is not supposed to model metabolism – it rather serves as a dynamic probe, meant to monitor the processing of perturbations (coming e.g. from concentration fluctuations) in the metabolic network. We analyze the emerging binary time series with entropy-like measures and find a reduced complexity for metabolic network structures when compared to different null model architectures. We argue that metabolic network topologies predominantly dampen perturbations (compared to randomized topologies) and therefore might contribute to the reliable establishment of steady states, the major mode of operation of real metabolism.

Contrary to our approach, Holme and Huss [2] model biochemical dynamics with enzyme kinetics. In order to apply the two-substrate Michaelis-Menten rate law they recreate a set of pairwise reactions from the substrate graphs of Ma and Zeng [3]. They compare the sets of recreated reactions with reactions generated from a null model graph with the same degree distribution and find no difference in the time evolution of the standard deviation of the metabolites' net fluxes. The authors claim that their finding contradicts our results, and conjecture the insignificance of the network structure to the stability of metabolic steady states [2].

The approach by Holme and Huss, however, has by construction no access to the topological information (i.e., larger-scale network properties beyond pairwise interactions) of interconnected metabolic reactions. Their algorithm to recreate reaction sets from graphs, combined with directed kinetics leads to a dynamical fragmentation of the graph. The information on the topology of metabolism is lost at this point of the investigation. We want to explain this in detail for the example of linear chains in the substrate graphs of Ma and Zeng (MZ) [3], which were used in both [1] and [2]. These chains represent the consecutive transformation of metabolites of the type A $\leftrightarrow$ B. They are ubiquitous in metabolism and constitute an important topological feature of the MZ metabolic networks. In most of these reactions, current metabolites (like ATP, ADP or H_20) act as carriers for electrons or functional groups, but have been removed from the MZ reaction database, due to an average path length rationale (see [3] for detailed explanations). The algorithm of Holme and Huss operates on the undirected MZ graphs assuming that most generating reactions are of the 2-1-form (A + B $\rightarrow$ C), or the 2-2-form (A + B $\rightarrow$ C + D). It thus converts a linear chain of connected metabolites to, at best, topologically connected reactions with defined directionality, as shown in Fig. 1. The imposed directionality, however, leads to a dynamical fragmentation, i.e. a network of dynamically isolated groups of nodes where the propaga-

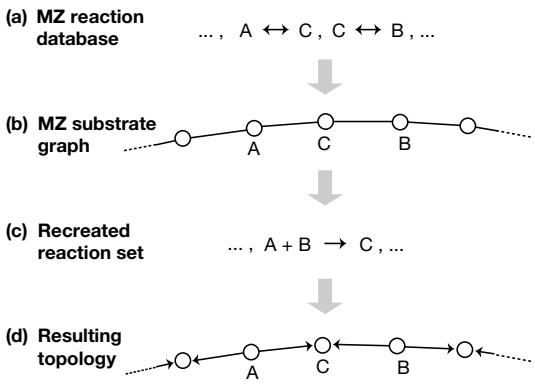

FIG. 1: The transformation of substrates in the presence of current metabolites (a) leads to a linear chains in the metabolic networks of Ma and Zeng (b). Via the algorithm in [2], the chain is converted into pairwise reactions of the form A + B $\rightarrow$ C (c). Together with the directionality of the fluxes imposed by the reaction kinetics, this leads to a dynamical fragmentation of the network. Transport is no longer possible along the resulting topology (d).

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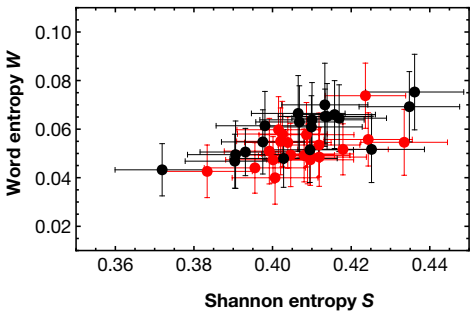

FIG. 2: The entropy signatures of 40 directed graphs. The entropy signatures of 'real' graphs (black) do not separate from those of the null model (red) in the entropy plane. All graphs have been reconstructed from the reaction sets used in [2], which in turn rely on the MZ substrate graph and randomized null models of the human metabolic network. Notably, we use the same parameters as in [1].

tion of information is no longer possible. Fig. 1 illustrates the generation of a chain from the MZ database and the loss of its information processing potential during the application of the algorithm of Holme and Huss. This network 'motif', a directed linear chain, therefore, cannot be represented with this approach. Note that dynamical fragmentation can still occur for more highly connected regions of a network. This effect induces the similarity in dynamics observed in [2] between the recreated metabolic networks and their randomized counterparts.

On the grounds of these topological observations, we would expect that our dynamic probe will also find no difference between the directed networks reconstructed from the reaction sets from Holme and Huss and the corresponding null model topologies. The algorithm from [2] provides a protocol to pass from an undirected graph to a reaction set. We use the standard protocol described in [3] to pass from this reaction set to a graph again. In their comment, the authors find no dynamical differences between the 'real' and their null model reaction systems. We implement our simple binary dynamics on the reconstructed directed graphs and, as expected, obtain similar entropy signatures for the respective topologies (see Fig. 2). The low entropy values, compared to the values of the metabolic networks shown in [1] are a consequence of spatiotemporal patterns of low complexity, which naturally arise from networks consisting of small fragments, where global information transport is suppressed.

Many aspects of the relationship between topology and dynamics are still unclear, especially when it comes to real systems. A fundamental question raised in [2] is, whether the entropy signature of a network is a meaningful observable or rather a data-mining tool. We acknowledge this criticism. Up to now, we cannot correlate the entropy measures with a clear biological quantity. Nevertheless, we are convinced that mapping out real network architectures with abstract dynamic probes, as described in [1], is a promising approach in order to understand the link between topology and dynamics. The question, if our dynamic probe is an appropriate surrogate for a network's response to fluctuations, however remains. It would thus be interesting to see the methodology of [2] applied to the original MZ reaction sets, or more appropriate network representations. In that respect, we agree with the call of Holme and Huss for a more detailed type of modeling.

We thank Niko Sonnenschein (Darmstadt) for valuable discussions.

[1] C. Marr, M. Müller-Linow, and M.-T. Hütt, Phys. Rev. E **75**, 041917 (2007).
[2] P. Holme and M. Huss, arXiv:0705.4084v1.
[3] H. Ma and A.-P. Zeng, Bioinformatics **19**, 270 (2003).